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1

☑ 2BUB

CRYSTAL STRUCTURE OF HUMAN DIPEPTIDYL PEPTIDASE IV (CD26) IN COMPLEX WITH A REVERSED AMIDE INHIBITOR

Characteristics **Release Date:** 23-Jan-2006 **Exp. Method:** X Ray Diffracti
Resolution: 2.66 Å

Classification **Complex (hydrolase/inhibitor)**

Compound **Mol. Id:** 1 **Molecule:** Dipeptidyl Peptidase 4 **Fragment:** E:
Domain Residues 39 766

Authors **Nordhoff, S., Cerezo-Galvez, S., Feurer, A., Hill O., Matassa, V.G., Metz, G., Rummey, C., Thien M., Edwards, P.J.**

☑ 1WCY

Crystal Structure Of Human Dipeptidyl Peptidase IV (DPPIV) Complex With Diproti A

Characteristics **Release Date:** 07-May-2005 **Exp. Method:** X Ray Diffracti
Resolution: 2.20 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Dipeptidyl Peptidase Iv **Fragment:** F
772 **Mol. Id:** 2 **Molecule:** Diprotin a

Authors **Hiramatsu, H., Yamamoto, A., Kyono, K., Higas Y., Fukushima, C., Shima, H., Sugiyama, S., In K., Shimizu, R.**

☑ 2BGR

CRYSTAL STRUCTURE OF HIV-1 TAT DERIVED NONAPEPTIDES TAT(1-9) BOUND TO THE ACTIVE SITE OF DIPEPTIDYL PEPTIDASE IV (CD26)

Characteristics **Release Date:** 27-Jan-2005 **Exp. Method:** X Ray Diffracti
Resolution: 2.00 Å

Classification **Hydrolase/complex**

Compound **Mol. Id:** 1 **Molecule:** Dipeptidyl Peptidase Iv **Fragment:** E
Domain Residues 29 766 **Mol. Id:** 2 **Molecule:** Hiv 1 Tat P
Derived N Terminal Nonapeptide

Authors **Weihofen, W.A., Liu, J., Reutter, W., Saenger, H.**

☑ 1W1I

CRYSTAL STRUCTURE OF DIPEPTIDYL PEPTIDASE IV (DPPIV OR CD26) IN COMPLEX WITH ADENOSINE DEAMINASE

Characteristics **Release Date:** 02-Sep-2004 **Exp. Method:** X Ray Diffracti

Classification **Resolution:** 3.03 Å
Hydrolase/complex

Compound **Mol. Id:** 1 **Molecule:** Dipeptidyl Peptidase Iv **Fragment:** E Domain 39 766 **Mol. Id:** 2 **Molecule:** Adenosine Deaminas

Authors **Weihofen, W.A., Liu, J., Reutter, W., Saenger, H.**

☑ **2BGN**

HIV-1 TAT PROTEIN DERIVED N-TERMINAL NONAPEPTIDE TRP2-TAT (1-9) BOUND TO THE ACTIVE SITE OF DIPEPTIDYL PEPTIDASE IV (CD26)

Characteristics **Release Date:** 27-Jan-2005 **Exp. Method:** X Ray Diffracti
Resolution: 3.15 Å

Classification **Hydrolase/complex**

Compound **Mol. Id:** 1 **Molecule:** Dipeptidyl Peptidase Iv **Fragment:** E Domain Residues 39 766 **Mol. Id:** 2 **Molecule:** Adenosine Deaminase **Mol. Id:** 3 **Molecule:** Tat Protein **Fragment:** Protein Derived N Terminal Nonapeptide Residues 1 9 **Mutati**

Authors **Weihofen, W.A., Liu, J., Reutter, W., Saenger, H.**

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Tuesday, June 06, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L12	(dipeptidyl peptidase IV or dipeptidylpeptidase IV or dipeptidyl peptidase-IV or dipeptidylpeptidase-IV or dpp-IV or dppIV or dpp IV) same (crystal or crystallization) and x-ray	3
		DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L11	(dipeptidyl peptidase IV or dipeptidylpeptidase IV or dipeptidyl peptidase-IV or dipeptidylpeptidase-IV or dpp-IV or dppIV or dpp IV) same (crystal or crystallization) and x-ray	4
☐	L10	(dipeptidyl peptidase IV or dipeptidylpeptidase IV or dipeptidyl peptidase-IV or dipeptidylpeptidase-IV or dpp-IV or dppIV or dpp IV)same crystal$9	27
☐	L9	(dipeptidyl adj1 peptidase adj1 IV or dpp adj1 IV)same crystal$9	25
☐	L8	(dipeptidyl adj1 peptidase adj1 IV or dpp adj2 IV)same crystal$9	25
		DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L7	L5 and x-ray	6
☐	L6	L5	38
☐	L5	(dipeptidyl adj1 peptidase adj1 IV or dpp adj2 IV)same crystal$9	38
☐	L4	(dipeptidylpeptidase adj3 IV or dpp adj2 IV)same crystal$9	28
		DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L3	L2	3
		DB=USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L2	(dipeptidylpeptidase adj3 IV or dpp adj2 IV)same crystal$9	3
		DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L1	(dipeptidyl adj3 peptidase adj3 IV or dpp adj3 IV)same crystal$9	25

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 6355614 B1

L11: Entry 1 of 4 File: USPT Mar 12, 2002

US-PAT-NO: 6355614
DOCUMENT-IDENTIFIER: US 6355614 B1

TITLE: Cyclic boroproline compounds

DATE-ISSUED: March 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wallner; Barbara P.	Weston	MA		

US-CL-CURRENT: 514/10; 514/249, 514/253.09

ABSTRACT:

Substantially pure preparations of cyclic boroProline compounds that bind, in cyclic or linear form, to CD26 are provided. Methods for using the cyclic compounds to stimulate the activation and/or proliferation of immune cells to achieve preselected normal in vivo levels of these cells also are provided. Evidence of the oral bioavailability and activity of a preferred cyclic compound, valine-prolineboronic acid (ValboroPro), also is provided.

8 Claims, 9 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: WO 2005119526 A1

L11: Entry 2 of 4 File: DWPI Dec 15, 2005

DERWENT-ACC-NO: 2006-066968
DERWENT-WEEK: 200607

TITLE: New crystalline composition of dipeptidyl peptidase IV, useful for treating diseases, e.g. diabetes, obesity, osteoporosis, arthritis, hypertension, atherosclerosis, ulcer, or inflammatory bowel syndrome

INVENTOR: QIU, X

PRIORITY-DATA: 2004US-576877P (June 3, 2004)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 2005119526 A1	December 15, 2005	E	151	G06F017/50

INT-CL (IPC): C07 K 14/00; G06 F 17/50

ABSTRACTED-PUB-NO: WO2005119526A
BASIC-ABSTRACT:

NOVELTY - A crystalline composition of the extracellular domain of mammalian dipeptidyl peptidase IV (DPP-IV) comprising one molecule per crystal asymmetric unit, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a polypeptide comprising the sequence of 766 amino acids (SEQ ID NO: 1) or its homologue or variant, where the molecules are arranged in a crystalline manner in a space group of P43212 so as to form a unit cell of dimensions a=b=68.7 Angstrom , c= 421.2 Angstrom and which diffracts X-rays for determination of the atomic coordinates of DPP-IV polypeptide to a resolution of 2.7 Angstrom ;

(2) a crystal of a protein-ligand molecule or molecular complex comprising: (i) a polypeptide with an amino acid sequence from Asp38 to Pro766 listed in SEQ ID NO: 1, or its homologue or variant; (ii) a ligand; and (iii) the crystal that diffracts X-rays for the determination of atomic coordinates of the protein-ligand complex to a resolution of greater than 2.7 Angstrom ;

(3) a method of designing a compound that binds to DPP-IV comprises the amino acid sequence spanning amino acids Gly31 to Pro766 listed in SEQ ID NO: 1, or its homologue or variant using the crystal above;

(4) a method for crystallizing a DPP-IV polypeptide molecule or molecular complex;

(5) a computer: (a) for producing a three-dimensional representation of a polypeptide with an amino acid sequence spanning amino acids Gly31 to Pro766 listed in SEQ ID NO: 1, or its homologue or variant; (b) for producing a three-dimensional representation of a molecule or molecular complex comprising the atomic coordinates having a root mean square deviation of less than 2.5, 2.0, 1.7, 1.5, 1.2, 1.0, 0.7, 0.5, or 0.2 Angstrom from the atomic coordinates for the carbon backbone atoms listed in the specification; or (c) for producing a three-dimensional representation of a molecule or molecular complex comprising a binding site defined by the structure coordinates given in the specification, or a the structural coordinates of a portion of the residues given in the specification, or the structural coordinates of one or more DPP-IV amino acids in SEQ ID NO: 1 selected from Glu205, Glu206, Tyr547, Ser630, Tyr631, Tyr662, Tyr666, Asp708, Asn710, or His740, the computer comprising: (i) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, where the data comprises the structure coordinates given in the specification, or their portions; (ii) a working memory for storing instructions for processing the computer-readable data; (iii) a central-processing unit coupled to the working memory and to the computer-readable data storage medium for processing the computer-machine readable data into the three-dimensional representation; and (iv) a display coupled to the central-processing unit for displaying the representation; and

(6) a method for identifying potential ligands for DPP-IV, or their homologues, analogues or variants.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Osteopathic; Antiarthritic; Neuroprotective; Nephrotropic; Ophthalmological; Hypotensive; Antiarteriosclerotic; Antiulcer; Gastrointestinal-Gen; Antiinflammatory.

No biological data given.

MECHANISM OF ACTION - DPP-Inhibitor-IV.

USE - The crystal, composition, and method are useful for treating diseases, e.g. diabetes, obesity, lipidemia, osteoporosis, arthritis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, hypertension, atherosclerosis, ulcer, or inflammatory bowel syndrome.

☐ 3. Document ID: JP 2004173695 A, EP 1422293 A1

L11: Entry 3 of 4 File: DWPI Jun 24, 2004

DERWENT-ACC-NO: 2004-413363
DERWENT-WEEK: 200441

TITLE: New crystal of an extracellular domain of mammalian dipeptidyl-peptidase IV (DPP-IV) useful for identifying or designing inhibitors of DPP-IV activity

INVENTOR: HENNIG, M; LOEFFLER, B M ; THOMA, R

PRIORITY-DATA: 2002EP-0026367 (November 25, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2004173695 A	June 24, 2004		214	C12N015/09
EP 1422293 A1	May 26, 2004	E	215	C12N009/48

INT-CL (IPC): A61 K 45/00; A61 P 3/04; A61 P 3/10; A61 P 35/00; C12 N 1/15; C12 N 1/19; C12 N 1/21; C12 N 5/10; C12 N 9/48; C12 N 15/09; C12 Q 1/37; G01 N 33/15; G01 N 33/50

ABSTRACTED-PUB-NO: EP 1422293A
BASIC-ABSTRACT:

NOVELTY - A crystal (I) of extracellular domain of mammalian dipeptidyl-peptidase (DPP)-IV, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a co-crystal of the extracellular domain of mammalian DPP-IV and a ligand bound to its active site;

(2) a co-crystal of the extracellular domain of mammalian DPP-IV and a ligand bound

to an allosteric binding site;

(3) a co-crystal of the extracellular domain of mammalian DPP-IV and HgCl2;

(4) crystallizing (M1) mammalian DPP-IV, involves providing a buffered aqueous solution of pH 7-8.5 with a concentration of 7-22 mg/ml of the extracellular domain of mammalian DPP-IV, and growing crystals by vapor diffusion using a buffered reservoir solution with between 10-30% PEG and between 10-20% glycerol, where PEG has an average molecular weight between 1000-20000;

(5) co-crystallizing (M2) mammalian DPPIV and an active site ligand, involves providing a buffered aqueous solution of pH 7-8.5 with a concentration of 7-22 mg/ml of the extracellular domain of mammalian DPP-IV, adding a molar excess of the active site ligand to the aqueous solution of mammalian DPP-IV, and growing crystals by vapor diffusion using a buffered reservoir solution with between 10-30% PEG and between 10-20% glycerol, where PEG has an average molecular weight between 1000 and 20000;

(6) a crystal produced by (M1) and (M2);

(7) determining the three-dimensional structure of a crystallized extracellular domain of mammalian DPP-IV to a resolution of 3.5-2.1 Angstrom or better, involves crystallizing an extracellular domain of mammalian DPP-IV, and analyzing the extracellular domain of mammalian DPP-IV by X-ray diffraction to determine the three-dimensional structure of the crystallized extracellular domain of mammalian DPP-IV, where the three-dimensional structure of a crystallized extracellular domain of mammalian DPP-IV is determined to a resolution of 3.5-2.1 Angstrom or better;

(8) a machine-readable data storage medium comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using the data, displays a graphical three-dimensional representation of a molecule or molecular complex comprising at least a portion of the extracellular domain of mammalian DPP-IV comprising a fully defined sequence (S1) of 736 amino acids as given in the specification, where the extracellular domain comprising the ligand binding active site being defined by a set of points having a root mean square deviation of less than about 1.5 Angstrom from points representing the backbone atoms of the amino acids as represented by structure coordinates as given in the specification;

(9) a compound (II) identified by using (I);

(10) a pharmaceutical composition (III) comprising (I) and a carrier;

(11) an isolated nucleic acid sequence (IV) encoding the soluble extracellular domain of DPP-IV comprising a fully defined sequence (S2) of 2211 amino acids as given in the specification;

(12) a nucleic acid construct (V) comprising an expression vector and (IV);

(13) a host cell (VI) transformed with (V);

(14) producing the soluble extracellular domain of DPP-IV, involves culturing (VI) under conditions permitting the expression of the soluble extracellular domain of DPP-IV by (VI); and

(15) a polypeptide comprising the soluble extracellular domain of (S1).

ACTIVITY - Antidiabetic; Anorectic; Cytostatic.

MECHANISM OF ACTION - Inhibitor of DPP-IV (claimed). No supporting data is given.

USE - (I) is useful for identifying a compound that interacts with DPP-IV which involves generating (I) (a three-dimensional model of DPP-IV using atomic structure coordinates for DPP-IV as derived by X-ray diffraction from a crystal of DPP-IV) and a root mean square deviation from the backbone atoms of the amino acids of less than 1.5 Angstrom , and employing the three-dimensional model to design or select a compound that interacts with DPP-IV. The above method further involves obtaining the identified compound, and contacting the obtained compound with DPP-IV in order to determine the effect the compound has on DPP-IV activity. The compound interacts with the active site of DPP-IV. The compound interacts with an allosteric binding site of DPP-IV. The compound is an inhibitor of DPP-IV activity. The method is a computer-assisted method. (I) is useful for the identification and/or design of inhibitors of DPP-IV activity. (II) is useful as a therapeutic active substance, in particular for the treatment of diabetes type I, diabetes type II, IGT, obesity and cancer. (II) is useful for the manufacture of a medicament for the treatment of above mentioned disease (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows overall structure of dipeptidyl-peptidase (DPP)-IV.

☐ 4. Document ID: JP 2005536995 W, WO 2004011640 A1, AU 2003253369 A1, EP 1525306 A1, US 20050260732 A1

L11: Entry 4 of 4 File: DWPI Dec 8, 2005

DERWENT-ACC-NO: 2004-156830
DERWENT-WEEK: 200580

TITLE: New crystal of dipeptidyl peptidase IV capable of analyzing its three-dimensional structure, useful for designing, identifying, evaluating or searching an effector of the dipeptidyl peptidase IV

INVENTOR: HIRAMATSU, H; KYONO, K ; SHIMA, H ; SUGIYAMA, S

PRIORITY-DATA: 2002US-398761P (July 29, 2002), 2005US-0522789 (January 28, 2005)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2005536995 W	December 8, 2005		110	C12N009/48
WO 2004011640 A1	February 5, 2004	E	342	C12N009/48
AU 2003253369 A1	February 16, 2004		000	C12N009/48
EP 1525306 A1	April 27, 2005	E	000	C12N009/48
US 20050260732 A1	November 24, 2005		000	C12N009/64

INT-CL (IPC): A61 K 45/00; A61 P 3/10; A61 P 19/02; A61 P 25/00; A61 P 29/00; A61 P 31/18; A61 P 35/00; A61 P 37/02; A61 P 43/00; C07 K 14/705; C12 N 9/48; C12 N 9/64; C12 N 15/09; C12 Q 1/37; G01 N 23/20; G01 N 33/15; G01 N 33/48; G01 N 33/50; G01 N 33/573; G06 F 19/00

ABSTRACTED-PUB-NO: WO2004011640A

BASIC-ABSTRACT:

NOVELTY - A crystal of a dipeptidyl peptidase IV, which is sufficient to ensure a resolution capable of analyzing its three-dimensional structure up to the side chain level by X-ray crystallographic structural analysis, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a three-dimensional structural coordinate of a dipeptidyl peptidase IV comprising the structural coordinate, which is fully defined in the specification or a structural coordinate different from the structural coordinate given in the specification;

(2) a three-dimensional structural coordinate of a region in a dipeptidyl peptidase IV comprising the three-dimensional structural coordinate of the region selected from: (a) the region of Ser 630, Asp 708 and His 740 in the amino acid sequence comprising 766 amino acids (SEQ ID NO. 2), and all or a part of a group of the amino acid residues located in the adjacent area of Ser 630, Asp 708 and His 740 in the structural coordinate given in the specification or the three-dimensional structure model defined by the structural coordinate; (b) the region of Ser 630, Asp 708 and His 740 in SEQ ID NO: 2, and all or a part of a group of the amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to each of amino acids in the group of the amino acid residues located in the adjacent area of Ser 630, Asp 708 and His 740; (c) the region of a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to Ser 630, Asp 708 and His 740 in SEQ ID NO: 2, and all or a part of a group of the amino acid residues located adjacent area of the group of the amino acid residues in the structural coordinate given in the specification or the three-dimensional structure model defined by the structural coordinate; and (d) the region of a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to Ser 630, Asp 708 and His 740 in SEQ ID NO: 2, and all or a part of a group of amino acid residues comprising amino acids capable of maintaining physicochemical characteristics physiologically equivalent to each of the amino acids in the group of the amino acid residues located in the adjacent area of the group of the amino acids, in the structural coordinate given in the specification or the three-dimensional structure model defined by the structural coordinate, wherein the region in the dipeptidyl peptidase IV is a region involved in binding or interaction between the dipeptidyl peptidase IV and an effector of the dipeptidyl peptidase IV;

(3) a method for obtaining a three-dimensional coordinate of a homologue protein of a dipeptidyl peptidase IV;

(4) a method for obtaining a three-dimensional structural coordinate of a crystal of a complex of a dipeptidyl peptidase IV and an effector of the dipeptidyl peptidase;

(5) a method for identifying pharmacophore of an effector of the dipeptidyl peptidase IV;

(6) a method for designing, identifying, evaluating or searching an effector of a dipeptidyl peptidase IV;

(7) an effector of the dipeptidyl peptidase IV obtainable by the method above; and

(8) a program and a medium for use of the three-dimensional structural coordinate, wherein all and/or a part of the three-dimensional structural coordinate is recorded.

ACTIVITY - Immunomodulatory; Antidiabetic; Antiinflammatory; Neuroprotective; Antithyroid; Antirheumatic; Antiarthritic; Anti-HIV; Cytostatic.

MECHANISM OF ACTION - Dipeptidyl peptidase IV effector.

USE - The crystal of a dipeptidyl peptidase IV is useful for providing a three-dimensional structural coordinate as the information for designing, identifying, evaluating or searching an effector of the dipeptidyl peptidase IV. The effector is useful as modulatory agent of immune response and as a therapeutic or prophylactic agent for diabetes, inflammation, multiple sclerosis, Graves' disease, chronic rheumatoid arthritis, AIDS or cancer.

Terms	Documents
(dipeptidyl peptidase IV or dipeptidylpeptidase IV or dipeptidyl peptidase-IV or dipeptidylpeptidase-IV or dpp-IV or dppIV or dpp IV) same (crystal or crystallization) and x-ray	4

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 20060024313 A1

L12: Entry 1 of 3 File: PGPB Feb 2, 2006

PGPUB-DOCUMENT-NUMBER: 20060024313
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060024313 A1

TITLE: Agents that disrupt dimer formation in DPP-IV family of prolyl dipeptidases

PUBLICATION-DATE: February 2, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Chen; Xin	Miaoli		TW
Chen; Yuan-Shou	Taipei City		TW

US-CL-CURRENT: 424/146.1; 435/226, 435/320.1, 435/325, 435/69.1, 530/388.26, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: US 20050261271 A1

L12: Entry 2 of 3 File: PGPB Nov 24, 2005

PGPUB-DOCUMENT-NUMBER: 20050261271
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050261271 A1

TITLE: Dipeptidyl peptidase inhibitors

PUBLICATION-DATE: November 24, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Feng, Jun	Carlsbad	CA	US
Gwaltney, Stephen L.	San Diego	CA	US
Stafford, Jeffrey A.	San Diego	CA	US
Zhang, Zhiyuan	San Diego	CA	US
Elder, Bruce J.	Wynantskill	NY	US
Isbester, Paul K.	Castleton	NY	US

Palmer, Grant J.	Clifton Park	NY	US
Salsbury, Jonathon S.	Albany	NY	US
Ulysse, Luckner G.	Albany	NY	US

US-CL-CURRENT: 514/210.2; 514/217.05, 514/217.06, 514/241, 514/275, 540/601, 544/209, 544/331

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 3. Document ID: US 20050260732 A1

L12: Entry 3 of 3 File: PGPB Nov 24, 2005

PGPUB-DOCUMENT-NUMBER: 20050260732
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050260732 A1

TITLE: Three-dimensional structure of dipeptidyl peptidase IV

PUBLICATION-DATE: November 24, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Hiramatsu, Hajime	Osaka		JP
Kyono, Kiyoshi	Osaka		JP
Shima, Hideaki	Hyogo		JP
Sugiyama, Shigeru	Nara		JP

US-CL-CURRENT: 435/226; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
(dipeptidyl peptidase IV or dipeptidylpeptidase IV or dipeptidyl peptidase-IV or dipeptidylpeptidase-IV or dpp-IV or dppIV or dpp IV) same (crystal or crystallization) and x-ray	3

Display Format: - Change Format

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FILE 'HOME' ENTERED AT 14:11:13 ON 06 JUN 2006

=> file .nash
=> s (dpp-IV or ddp IV or dppiv) and crystal?
L1          25 FILE MEDLINE
L2          37 FILE CAPLUS
L3          36 FILE SCISEARCH
L4           2 FILE LIFESCI
L5          18 FILE BIOSIS
L6          19 FILE EMBASE

TOTAL FOR ALL FILES
L7         137 (DPP-IV OR DDP IV OR DPPIV) AND CRYSTAL?

=> s l7 not 2004-2006/py
TOTAL FOR ALL FILES
L14         33 L7 NOT 2004-2006/PY

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15          12 DUP REM L14 (21 DUPLICATES REMOVED)

=> d ibib abs 1-12

L15  ANSWER 1 OF 12     MEDLINE on STN
ACCESSION NUMBER:   2003275428     MEDLINE Full-text
DOCUMENT NUMBER:    PubMed ID: 12801240
TITLE:              1-[[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-
                    pyrrolidine: a potent, selective, and orally bioavailable
                    dipeptidyl peptidase IV inhibitor with antihyperglycemic
                    properties.
AUTHOR:             Villhauer Edwin B; Brinkman John A; Naderi Goli B; Burkey
                    Bryan F; Dunning Beth E; Prasad Kapa; Mangold Bonnie L;
                    Russell Mary E; Hughes Thomas E
CORPORATE SOURCE:   Novartis Institute for Biomedical Research, One Health
                    Plaza, East Hanover, New Jersey 07936, USA..
                    edwin.villhauer@pharma.novartis.com
SOURCE:             Journal of medicinal chemistry, (2003 Jun 19) Vol. 46, No.
                    13, pp. 2774-89.
                    Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200307
ENTRY DATE:         Entered STN: 13 Jun 2003
                    Last Updated on STN: 16 Jul 2003
                    Entered Medline: 15 Jul 2003
AB     Dipeptidyl peptidase IV (DPP-IV) inhibition has the potential to become a valuable therapy
       for type 2 diabetes.  The synthesis and structure-activity relationship of a new DPP-IV
       inhibitor class, N-substituted-glycyl-2-cyanopyrrolidines, are described as well as the
       path that led from clinical development compound 1-[2-[5-cyanopyridin-2-
       yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728, 8c) to its follow-up, 1-
       [[(3-hydroxy-1-adamantyl) amino]acetyl]-2-cyano-(S)-pyrrolidine (NVP-LAF237, 12j).  The
       pharmacological profile of 12j in obese Zucker fa/fa rats along with pharmacokinetic
       profile comparison of 8c and 12j in normal cynomolgus monkeys is discussed.  The results
       suggest that 12j is a potent, stable, selective DPP-IV inhibitor possessing excellent oral
       bioavailability and potent antihyperglycemic activity with potential for once-a-day
       administration.


L15  ANSWER 2 OF 12     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2003373331     MEDLINE Full-text
DOCUMENT NUMBER:    PubMed ID: 12906826
TITLE:              Structural basis of proline-specific exopeptidase activity
                    as observed in human dipeptidyl peptidase-IV.
AUTHOR:             Thoma Ralf; Loffler Bernd; Stihle Martine; Huber Walter;
                    Ruf Armin; Hennig Michael
CORPORATE SOURCE:   F. Hoffmann-La Roche AG, Pharma Research Discovery, 4070
                    Basel, Switzerland.
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SOURCE: Structure (Cambridge, Mass. : 2001), (2003 Aug) Vol. 11, No. 8, pp. 947-59.
Journal code: 101087697. ISSN: 0969-2126.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1NU6; PDB-1NU8
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 9 Aug 2003
Last Updated on STN: 15 Apr 2004
Entered Medline: 14 Apr 2004

AB Inhibition of dipeptidyl peptidase IV (DPP-IV), the main glucagon-like peptide 1 (GLP1)-degrading enzyme, has been proposed for the treatment of type II diabetes. We expressed and purified the ectodomain of human DPP-IV in Pichia pastoris and determined the X-ray structure at 2.1 A resolution. The enzyme consists of two domains, the catalytic domain, with an alpha/beta hydrolase fold, and a beta propeller domain with an 8-fold repeat of a four-strand beta sheet motif. The beta propeller domain contributes two important functions to the molecule that have not been reported for such structures, an extra beta sheet motif that forms part of the dimerization interface and an additional short helix with a double Glu sequence motif. The Glu motif provides recognition and a binding site for the N terminus of the substrates, as revealed by the complex structure with diprotin A, a substrate with low turnover that is trapped in the tetrahedral intermediate of the reaction in the crystal.

L15 ANSWER 3 OF 12 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003132018 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12646248
TITLE: The structure and function of human dipeptidyl peptidase IV, possessing a unique eight-bladed beta-propeller fold.
AUTHOR: Hiramatsu Hajime; Kyono Kiyoshi; Higashiyama Yutaka; Fukushima Chiaki; Shima Hideaki; Sugiyama Shigeru; Inaka Koji; Yamamoto Atsushi; Shimizu Ryo
CORPORATE SOURCE: Discovery Research Laboratory, Tanabe Seiyaku Co. Ltd., 3-16-86 Kashima, Yodogawa-ku, Osaka 532-8505, Japan.
SOURCE: Biochemical and biophysical research communications, (2003 Mar 21) Vol. 302, No. 4, pp. 849-54.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 21 Mar 2003
Last Updated on STN: 14 May 2003
Entered Medline: 13 May 2003

AB Dipeptidyl peptidase IV (DPPIV) is a serine protease, a member of the prolyl oligopeptidase (POP) family, and has been implicated in several diseases. Therefore, the development of DPPIV selective inhibitors, which are able to control the biological function of DPPIV, is important. We determined the crystal structure of human DPPIV at 2.6A resolution. The molecule consists of a unique eight-bladed beta-propeller domain in the N-terminal region and a serine protease domain in the C-terminal region. Also, the large "cave" structure, which is thought to control the access of the substrate, is found on the side of the beta-propeller fold. Comparison of the overall amino acid sequence between human DPPIV and POP shows low homology (12.9%). In this paper, we report the structure of human DPPIV, especially focusing on a unique eight-bladed beta-propeller domain. We also discuss the way for the access of the substrate to this domain.

L15 ANSWER 4 OF 12 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003083668 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12595736
TITLE: Crystallization and preliminary X-ray study of human dipeptidyl peptidase IV (DPPIV).
AUTHOR: Hiramatsu Hajime; Kyono Kiyoshi; Shima Hideaki; Fukushima Chiaki; Sugiyama Shigeru; Inaka Koji; Yamamoto Atsushi; Shimizu Ryo
CORPORATE SOURCE: Discovery Research Laboratory, Tanabe Seiyaku Co. Ltd, 3-16-89 Kashima, Yodogawa-ku, Osaka 532-8505, Japan.
SOURCE: Acta crystallographica. Section D, Biological

crystallography, (2003 Mar) Vol. 59, No. Pt 3, pp. 595-6.
Electronic Publication: 2003-02-21.
Journal code: 9305878. ISSN: 0907-4449.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 22 Feb 2003
Last Updated on STN: 8 Oct 2003
Entered Medline: 7 Oct 2003

AB Human DPPIV has been expressed in the baculovirus system and purified and crystallized using the hanging-drop method. A crystal was obtained from 180 mM Gly-NaOH buffer pH 9.5 containing 18% PEG 4000 and 180 mM sodium acetate. The crystal belongs to the orthorhombic space group P2(1)2(1)2(1), with unit-cell parameters a = 118.04, b = 125.92, c = 136.84 A, and diffracts beyond 2.6 A resolution. There are two molecules per asymmetric unit, indicating a solvent content of 57.6%.

L15 ANSWER 5 OF 12 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002728574 IN-PROCESS Full-text
DOCUMENT NUMBER: PubMed ID: 12483204
TITLE: Crystal structure of human dipeptidyl peptidase IV/CD26 in complex with a substrate analog.
AUTHOR: Rasmussen Hanne B; Branner Sven; Wiberg Finn C; Wagtmann Nicolai
CORPORATE SOURCE: Protein Chemistry, Research and Development, Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark.
SOURCE: Nature structural biology, (2003 Jan) Vol. 10, No. 1, pp. 19-25.
Journal code: 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20 Dec 2002
Last Updated on STN: 17 Dec 2003

AB Dipeptidyl peptidase IV (DPP-IV/CD26) is a multifunctional type II transmembrane serine peptidase. This enzyme contributes to the regulation of various physiological processes, including blood sugar homeostasis, by cleaving peptide hormones, chemokines and neuropeptides. We have determined the 2.5 A structure of the extracellular region of DPP-IV in complex with the inhibitor valine-pyrrolidide. The catalytic site is located in a large cavity formed between the alpha/beta-hydrolase domain and an eight-bladed beta-propeller domain. Both domains participate in inhibitor binding. The structure indicates how substrate specificity is achieved and reveals a new and unexpected opening to the active site.

L15 ANSWER 6 OF 12 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002426880 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12182835
TITLE: Expression, purification, and characterization of human dipeptidyl peptidase IV/CD26 in Sf9 insect cells.
AUTHOR: Dobers Jorg; Zimmermann-Kordmann Martin; Leddermann Melanie; Schewe Tina; Reutter Werner; Fan Hua
CORPORATE SOURCE: Institut fur Molekularbiologie und Biochemie, Fachbereich Humanmedizin, Freie Universitat Berlin, Arnimallee 22, D-14195 Berlin-Dahlem, Germany.
SOURCE: Protein expression and purification, (2002 Aug) Vol. 25, No. 3, pp. 527-32.
Journal code: 9101496. ISSN: 1046-5928.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 17 Aug 2002
Last Updated on STN: 13 Mar 2003
Entered Medline: 12 Mar 2003

AB The human dipeptidyl peptidase IV/CD26 (DPPIV/CD26) is a multifunctional type-II membrane bound glycoprotein. As a receptor of collagen I and fibronectin it mediates cell-cell and cell-matrix adhesion, and by interacting with extracellular adenosine deaminase and CD45 it is involved in regulatory and costimulatory events in the immune system. DPPIV/CD26 has a very distinct substrate specificity, and is potentially capable of truncating many cytokines, chemokines, and peptide hormones. In this study, we describe the overexpression, purification, and characterization of human DPPIV/CD26 in Spodoptera frugiperda (Sf9) cells, using the baculovirus system. Overexpression of DPPIV/CD26 was confirmed by measurement of its peptidase specificity, SDS-PAGE, and Western blot analyses. Expression rates were between 6.4 and 17.6 mg protein per liter suspension culture (1.5 x 10(9)cells). The N-linked oligosaccharide composition was examined and compared with that of mammalian cell-expressed DPPIV/CD26. Two-step purification by immunoaffinity chromatography and size-exclusion fast protein liquid chromatography (SE-FPLC) led to highly stable protein with significant peptidase activity. A subsequent gel filtration step on a Superdex 200 column yielded 2mg homogeneous dimeric DPPIV/CD26 (per liter insect cell culture) for crystallographic studies. Protein homogeneity was confirmed by silver staining of non-denaturating PAGE gels and by MALDI-TOF analysis of tryptic peptides.

L15 ANSWER 7 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:302127 SCISEARCH Full-text
THE GENUINE ARTICLE: 536QM
TITLE: Threading with chemostructural restrictions method for predicting fold and functionally significant residues: Application to dipeptidylpeptidase IV (DPP-IV)
AUTHOR: Reva B (Reprint); Finkelstein A; Topiol S
CORPORATE SOURCE: Discovery Partners Int, Computat Div, Suite 645, 2 Execut Dr, Ft Lee, NJ 07024 USA (Reprint); Novartis Inst Biomed Res, Summit, NJ USA; Russian Acad Sci, Inst Prot Res, Pushchino 142292, Moscow Region, Russia
COUNTRY OF AUTHOR: USA; Russia
SOURCE: PROTEINS-STRUCTURE FUNCTION AND GENETICS, (1 MAY 2002) Vol. 47, No. 2, pp. 180-193.
ISSN: 0887-3585.
PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 52
ENTRY DATE: Entered STN: 19 Apr 2002
Last Updated on STN: 19 Apr 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

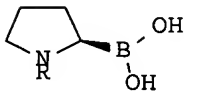
AB We present a new method for more accurate modeling of protein structure, called threading with chemostructural restrictions. This method addresses those cases in which a target sequence has only remote homologues of known structure for which sequence comparison methods cannot provide accurate alignments. Although remote homologues cannot provide an accurate model for the whole chain, they can be used in constructing practically useful models for the most conserved-and often the most interesting-part of the structure. For many proteins of interest, one can suggest certain chemostructural patterns for the native structure based on the available information on the structural superfamily of the protein, the type of activity, the sequence location of the functionally significant residues, and other factors. We use such patterns to restrict (1) a number of possible templates, and (2) a number of allowed chain conformations on a template. The latter restrictions are imposed in the form of additional template potentials (including terms acting as sequence anchors) that act on certain residues. This approach is tested on remote homologues of alpha/beta-hydrolases that have significant structural similarity in the positions of their catalytic triads. The study shows that, in spite of significant deviations between the model and the native structures, the surroundings of the catalytic triad (positions of C-alpha atoms of 20-30 nearby residues) can be reproduced with accuracy of 2-3 Angstrom. We then apply the approach to predict the structure of dipeptidylpeptidase IV (DPP-IV). Using experimentally available data identifying the catalytic triad residues of DPP- IV (David et al., J Biol Chem 1993;268:1724717252); we predict a model structure of the catalytic domain of DPP-TV based on the 3D fold of prolyl oligopeptidase (Fulop et al., Cell 1998;94:161-170) and use this structure for modeling the interaction of DPP-IV with inhibitor.

L15 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:723704 CAPLUS Full-text
DOCUMENT NUMBER: 136:2627
TITLE: Sulphostin, a potent inhibitor for dipeptidyl peptidase IV from Streptomyces sp. MK251-43F3
AUTHOR(S): Akiyama, Tetsuo; Abe, Masatoshi; Harada, Shigeko; Kojima, Fukiko; Sawa, Ryuichi; Takahashi, Yoshikazu; Naganawa, Hiroshi; Homma, Yoshiko; Hamada, Masa; Yamaguchi, Akihito; Aoyagi, Takaaki; Muraoka, Yasuhiko; Takeuchi, Tomio
CORPORATE SOURCE: Institute of Microbial Chemistry, Tokyo, 141-0021, Japan
SOURCE: Journal of Antibiotics (2001), 54(9), 744-746
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The production, isolation, and structure elucidation of isolated sulfostin (1) and its epimer were presented. Sulfostin was isolated from the culture broth of Streptomyces sp. MK251-43F3 together with its epimer, which was found to be formed during the isolation process. The fermentation process of producing sulfostin was extremely hard due to low productivity, tedious isolation procedure, and unavoidable epimerization during the isolation process. Chemical syntheses of sulfostin and its three diastereomers was successfully obtained. The X-ray crystal anal. of synthesized 1 showed that the absolute configurations of the C-3 and the phosphorus atoms of 1 were S and R, resp. The structure of sulfostin was found to be 3(S)-amino-1-[(R)-amino(sulfoamino)phosphinyl]-2-piperidone. Sulfostin showed inhibitory activities of dipeptidyl peptidase IV (DPPIV) with dose-dependent manner, and the IC50 value was 6 ng/mL, which was determined to be 100-fold stronger than that of diprotin A (a known DPP -IV inhibitor).
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999045629 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9826645
TITLE: Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics.
AUTHOR: Lin J; Toscano P J; Welch J T
CORPORATE SOURCE: Department of Chemistry, University at Albany, Albany, NY 12222, USA.
CONTRACT NUMBER: A133690
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1998 Nov 24) Vol. 95, No. 24, pp. 14020-4.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 28 Dec 1998
AB Dipeptidyl peptidase IV (EC 3.4.14.5; DPP IV), also known as the leukocyte differentiation antigen CD26 when found as an extracellular membrane-bound proline specific serine protease, cleaves a dipeptide from the N terminus of a polypeptide chain containing a proline residue in the penultimate position. Here we report that known (Z)-Ala-psi[CF=C]-Pro dipeptide isosteres 1 and 2, which contain O-acylhydroxylamines, were isolated as diastereomeric pairs u-1, l-1, and l-2. The effect of each diastereomeric pair as an inhibitor of human placental dipeptidyl peptidase DPP IV has been examined. The inhibition of DPP IV by these compounds is rapid and efficient. The diastereomeric pair u-1 exhibits very potent inhibitory activity with a Ki of 188 nM. Fluoroolefin containing N-peptidyl-O-hydroxylamine peptidomimetics, by virtue of their inhibitory potency and stability, are superior to N-peptidyl-O-hydroxylamine inhibitors derived from an Ala-Pro dipeptide.

L15 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1995:183432 CAPLUS Full-text

DOCUMENT NUMBER: 122:240402
TITLE: Studies on Proline Boronic Acid Dipeptide Inhibitors of Dipeptidyl Peptidase IV: Identification of a Cyclic Species Containing a B-N Bond
AUTHOR(S): Snow, Roger J.; Bachovchin, William W.; Barton, Randall W.; Campbell, Scot J.; Coutts, Simon J.; Freeman, Dorothy M.; Gutheil, William G.; Kelly, Terence A.; Kennedy, Charles A.; et al.
CORPORATE SOURCE: Department of Medicinal Chemistry Pharmacology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, 06877, USA
SOURCE: Journal of the American Chemical Society (1994), 116(24), 10860-9
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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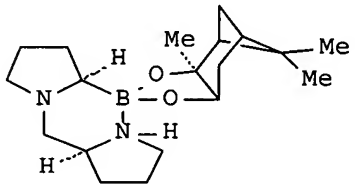

II

AB The proline boronic acid dipeptides I (R = H-Ala, H-Pro, H-Val) are very potent inhibitors of the enzyme dipeptidyl peptidase IV (DPP IV or CD26), found on the surface of T-cells, and are a new class of immunosuppressants. The efficient synthesis of the free boronic acids as single enantiomers is described, and the absolute configuration determined I lose DPP IV inhibitory activity in solution: this is shown to be due to the reversible formation of a cyclic species analogous to a diketopiperazine, containing a B-N bond. The cyclic compds., both as the free boronic acids and as the pinanediol esters, were isolated and characterized by 1H and 11B NMR, and in the case of II, by x-ray crystallog. The cyclization is pH dependent, with the open form favored at low pH, while the cyclic form predominates at neutral pH. Both the rate and extent of cyclization depend on the N-terminal amino acid. The rates of cyclization have been measured by 1H NMR and shown to correlate with the decrease in DPP IV inhibitory activity. I (R = H-Val) cyclizes more slowly, and to a lesser extent than I (R = H-Ala, H-Pro), which is predicted to lead to greater immunosuppressive potency in vivo.

L15 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:456711 CAPLUS Full-text
TITLE: Discovery, Structure-Activity Relationship, and Pharmacological Evaluation of (5-Substituted-pyrrolidinyl-2-carbonyl)-2-cyanopyrrolidines as Potent Dipeptidyl Peptidase IV Inhibitors
AUTHOR(S): Pei, Zhonghua; Li, Xiaofeng; Longenecker, Kenton; von Geldern, Thomas W.; Wiedeman, Paul E.; Lubben, Thomas H.; Zinker, Bradley A.; Stewart, Kent; Ballaron, Stephen J.; Stashko, Michael A.; Mika, Amanda K.; Beno, David W. A.; Long, Michelle; Wells, Heidi; Kempf-Grote, Anita J.; Madar, David J.; McDermott, Todd S.; Bhagavatula, Lakshmi; Fickes, Michael G.; Pireh, Daisy; Solomon, Larry R.; Lake, Marc R.; Edalji, Rohinton; Fry, Elizabeth H.; Sham, Hing L.; Trevillyan, James M.
CORPORATE SOURCE: Metabolic Disease Research, Advanced Technology, Departments of Exploratory Pharmacokinetics and Pharmaceutics and Process Chemistry Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA

SOURCE: Journal of Medicinal Chemistry ACS ASAP
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of (5-substituted pyrrolidinyl-2-carbonyl)-2-cyanopyrrolidine (C5-Pro-Pro) analogs was discovered as dipeptidyl peptidase IV (DPPIV) inhibitors as a potential treatment of diabetes and obesity. X-ray crystallog. data show that these inhibitors bind to the catalytic site of DPPIV with the cyano group forming a covalent bond with the serine residue of DPPIV. The C5-substituents make various interactions with the enzyme and affect potency, chemical stability, selectivity, and PK properties of the inhibitors. Optimized analogs are extremely potent with subnanomolar Ki's, are chemical stable, show very little potency decrease in the presence of plasma, and exhibit more than 1,000-fold selectivity against related peptidases. The best compds. also possess good PK and are efficacious in lowering blood glucose in an oral glucose tolerance test in ZDF rats.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:492547 CAPLUS Full-text
TITLE: Crystal Structures of DPP-IV (CD26) from Rat Kidney Exhibit Flexible Accommodation of Peptidase-Selective Inhibitors
AUTHOR(S): Longenecker, Kenton L.; Stewart, Kent D.; Madar, David J.; Jakob, Clarissa G.; Fry, Elizabeth H.; Wilk, Sherwin; Lin, Chun W.; Ballaron, Stephen J.; Stashko, Michael A.; Lubben, Thomas H.; Yong, Hong; Pireh, Daisy; Pei, Zhonghua; Basha, Fatima; Wiedeman, Paul E.; von Geldern, Thomas W.; Trevillyan, James M.; Stoll, Vincent S.
SOURCE: Biochemistry ACS ASAP
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dipeptidyl peptidase IV (DPP-IV) belongs to a family of serine peptidases, and due to its indirect regulatory role in plasma glucose modulation, DPP-IV has become an attractive pharmaceutical target for diabetes therapy. DPP-IV inactivates the glucagon-like peptide (GLP-1) and several other naturally produced bioactive peptides that contain preferentially a proline or alanine residue in the second amino acid sequence position by cleaving the N-terminal dipeptide. To elucidate the details of the active site for structure-based drug design, we crystallized a natural source preparation of DPP-IV isolated from rat kidney and determined its three-dimensional structure using X-ray diffraction techniques. With a high degree of similarity to structures of human DPP-IV , the active site architecture provides important details for the design of inhibitory compds., and structures of inhibitor-protein complexes offer detailed insight into three-dimensional structure-activity relationships that include a conformational change of Tyr548. Such accommodation is exemplified by the response to chemical substitution on 2-cyanopyrrolidine inhibitors at the 5 position, which conveys inhibitory selectivity for DPP-IV over closely related homologues. A similar conformational change is also observed in the complex with an unrelated synthetic inhibitor containing a xanthine core that is also selective for DPP-IV. These results suggest the conformational flexibility of Tyr548 is unique among protein family members and may be utilized in drug design to achieve peptidase selectivity.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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